COMPARISON OF VARIOUS PROSTAGLANDINS FOR INDUCTION OF ABORTION, MISSED LABOUR AND FOR TREATMENT OF POST-PARTUM ATONY

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When prostaglandins (PGs) were introduced in clinical medicine in the late 1960s, there were good hopes that these novel drugs would revolutionize the entire field of reproduction and fertility regulation. While it is clear that this has not been the case, their impact has nonetheless been substantial. In pregnancy, their effects encompass three different mechanisms: luteolysis, uterine stimulation and cervical compliance, but only the last two can be successfully influenced in man. Although all clinical use of PGs thus aims to pharmacologically influence either one or both of these mechanisms, the goals that need to be achieved and the available means have hitherto resulted in six different types of application: 1) induction of labour; 2) pre-labour cervical ripening; 3) pre-operative cervical dilatation; 4) induced abortion; 5) management of antepartum fetal death; and 6) postpartum uterine atony. Despite the fact that this subdivision of clinical uses contains several elements of artificiality, there are sound clinical reasons for considering each of these as a distinct entity. While the applications which are considered in this presentation are not the most frequent ones, in our opinion they contain the two most important contributions of PGs to clinical obstetrics: management of fetal death and of uterine atony.

Induction of abortion and pre-operative cervical dilatation

In the first trimester, none of the known PG regimens can match the convenience and acceptability of vacuum aspiration under local anaesthesia. Moreover, PGs do not preclude the need for vacuum aspiration, since the incidence of incomplete abortion (20 to 50+ % depending on method and gestational age) is high enough to warrant mechanical evacuation in all cases. Despite the vaste literature on pre-operative dilatation with various PGs in early pregnancy, it is dubious whether cost-benefit analyses could sustain claims that such procedures should henceforth be adopted for routine use. Nevertheless, selective use of PGs to lower cervical resistance in women with an unyielding and rigid cervix is likely to be superior to forceful dilatation, although the choice of PG and the dose and route of administration cannot be fixed at present. High success rates in a reasonably short interval of 3-4 hours can be achieved with vaginal 0.5-1 mg suppositories of 16,16-dimethyl-PGE analogues, with 500 µg (or possibly 250 µg) sulprostone intramuscularly or 25 µg sulprostone intra-cervically (injected 3-4 cm deep in the cervical tissues).

PGs have established a major role in terminating second trimester pregnancy, but successful application depends on a large number of variables (Table I). Systemic administration of natural PGs is now obsolete. Intra-amniotic administration of PGE2 and PGF2α is only suitable beyond 15 weeks and requires either high doses or repeat injections to achieve reasonable success. Gastrointestinal side

side effects, risk of cervical injuries and the need for enhancement with oxytocin are serious limitations. Extra-amniotic instillation of 200 µg PGE2 or 750 µg PGF2α two-hourly or equivalent amounts by continuous infusion result in a high success rate with a low incidence of side effects, but oxytocin may be needed in up to 50 % of patients and the method is rather cumbersome. The use of a viscous gel (e.g. with 2-3 mg PGE2) limits the need for frequent or continuous dosage, but mostly a repeat dose or oxytocin remain required. Natural PGs have therefore been largely replaced by analogues, although much depends on the availability. The main reasons have been: resistance to degradation by 15-hydroxy-prostaglandin dehydrogenase (which results in longer half-life and better systemic administration) and higher uterospecificity. Many analogues have been tested, but of those currently available in Europe, sulprostone (multi-substituted PGE2 analogue) appears to be the best choice. So far, it is not clear whether the recommended doses of 0.5 mg i.m. every 4 hrs, 1.5 mg i.v. during 6 hrs or 1.0 mg i.v. during 10 hrs provide ideal dose schedules. The cumulative experience may well contain a plea for examining lower and less arbitrary dose schedules.

TABLE I – Variables known to influence the effectiveness, complication rate and incidence of side effects of termination of pregnancy with prostaglandins.

1. Nature of the prostaglandin (E_2, $F_{2\alpha}$, analogue)
2. Dose used
3. Preparation used (solution, pessary, gel, ...)
4. Route of administration – systemic (vaginal, intravenous, intramuscular, ...) – local (intraamniotic, extraamniotic)
5. Frequency of administration (single dose, repeat, continuous, ...)
6. Augmentation with other methods (laminaria tents, oxytocin infusion, intraamniotic urea or saline, ...)
7. Type of pregnancy (viable pregnancy, molar pregnancy, intrauterine fetal death)
8. Gestational age

Management of antepartum fetal death

Fetal death now occurs on average earlier in pregnancy and is diagnosed more readily, thereby increasing the need for effective termination. PGs will terminate such pregnancies more readily (shorter interval; lower dose) than viable pregnancies of similar duration. Nevertheless the disadvantages of natural PGs still apply. Oral and vaginal routes require an advanced gestational age, some spontaneous contractility or a ripe cervix to overcome ineffectiveness and side effects. Intra-amniotic instillation is unsafe. Extra-amniotic administration combines high efficacy with few side effects but can be cumbersome. Several analogues have shown a high effectiveness but there has been little attention to optimal dosage and most studies have undoubtedly used excessive doses and/or irrational schedules of administration. Presently, there is a near 100 % chance of induction-delivery intervals < 24 hours with i.m. injections of 15-methyl-PGF2α (250 µg/2 hrs) or sulprostone

(500 µg/4-6 hrs), though side effects are less prominent with the latter. In multiparous women 125 µg 15-me-PGF2α is at least as effective as 250 µg. With pharmacological data, this indicates that recommended doses of both, and sulprostone in particular may be well in excess of what is required. Similarly, for adequate efficacy i.v. infusion rates of sulprostone should probably never exceed 2 µg/min.

Postpartum haemorrhage due to uterine atony

Since Tagaki et al. pioneered the use of PGs to control moderate to severe postpartum bleeding, there have been numerous reports on the successes that have been achieved with various PGs administered by various routes. The former have included PGE2, PGF2α, 15-me-PGF2α, sulprostone and the latter include i.m., i.v., vaginal, intra-cavitary, intra-cervical and intra-myometrial via abdominal or vaginal routes. All reports have dealt with a few cases at most; negative results are unlikely to be reported or published; and there are hitherto no randomized controlled trials (one trial using the prophylactic approach showed 250 µg 15-me-PGF2α i.m. to be more effective than 125 or 62.5 µg but with significant gastro-intestinal side effects). Despite this lack of controlled data, in many instances, including our own experience, PGs were resorted to as ultimate step prior to radical surgery. Not surprisingly in these circumstances an incredible dose range has been used. While emphasizing the uncontrolled nature of the data and the need for an adequately controlled trial, on the basis of the available data it may be tentatively concluded that intramyometrial injection (either at caesarean section, transabdominally or vaginally in the lower segment) of 250 µg sulprostone, 125 µg 15-me-PGF2α or 1000 µg PGF2α may control severe postpartum haemorrhage caused by uterine atony. At the same time, comparison of these dosages of different PGs should indicate the ad hoc nature of that conclusion.

Conclusion:

Unfortunately, comparison of various PGs for the indications discussed above still shows major limitations. On the one hand, this is due to heterogeneity of parameters such as gastrointestinal side effects, percentage of success, time interval required to achieve such success, potential or real hazards, etc. all of which may be valued differently and are difficult to weigh against each other. On the other hand, the main causes still relate to the availability of PGs with different compounds being available in different countries. Rational choice of future therapies will obviously require a solution to such problems.